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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/519,813 | 12/27/2004 | Hiroyuki Hashimoto | CFO17350WOUS | 5411 |

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| EXAMINER | |
|---|---|
| STRZELECKA, TERESA E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 02/01/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/519,813 | HASHIMOTO ET AL. | |
| | Examiner | Art Unit | |
| | TERESA E. STRZELECKA | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *4,6,9,10,13,14 and 16-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,8,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 4, 2009 has been entered.

2. Claims 1-56 were previously pending, with claims 4, 6, 9, 10, 13, 14, 16-29, 32, 34, 37, 38, 41, 43 and 48-56 withdrawn from consideration. Applicants amended claims 1, 2, 12 and 15 and cancelled claims 30-56. Claims 1-29 are pending, with claims 4, 6, 9, 10, 13, 14 and 16-29 withdrawn from consideration. Applicants' amendments overcame the rejection of claims 1-3, 5, 7, 8, 11, 12, 15, 30, 31, 33, 35, 36, 39, 40, 42 and 44-47 under 35 U.S.C. 103(a) as being unpatentable over Okamoto et al., Park, Rava et al., Sundberg et al., Strother et al., Corn et al. and Maxim et al.

3. This office action contains new grounds for rejection necessitated by amendment.

### *Information Disclosure Statement*

4. The information disclosure statement (IDS) submitted on August 27, 2009 was filed after the mailing date of the final office action on July 25, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, 7, 8, 11, 12 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 recites a limitation "said plural probe solutions" in step (8-2). There is insufficient antecedent basis for this limitation in the claim. Step (a) of the claim has been amended to recite "100 or more kinds of purified probes".

B) Claim 2 recites the limitation "the plural probe solution" in step (j-2). There is insufficient antecedent basis for this limitation in the claim. Step (a) of the claim has been amended to recite "100 or more kinds of probes".

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 5, 7, 8, 11, 12 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okamoto et al. (Nature Biotechnol., vol. 18, pp. 438-441, 2000; cited in the IDS and in the previous office action), Chen et al. (WO 01/62378; cited in the IDS), Silverbrook (U.S. Patent No. 5,815,173 A), Park (U.S. Patent No. 6,839,454 B1; cited in the previous office action), Rava et al. (WO 99/39817; cited in the IDS and in the previous office action), Sundberg et al. (U.S. Patent No. 5,624,711 A; cited in the previous office action), Strother et al. (U.S. Patent No. 6,569,979 B1; cited in the previous office action), Corn et al. (U.S. Patent No. 6,127,129 A; cited in the previous office action) and Maxim et al. (U.S. Patent No. 7,191,901 B2; cited in the previous office action).

Claims 1, 2, 11, 12 and 15 will be considered together in claim 2, since it is a species of claims 1, 11, 12 and 15.

A) Regarding claims 1, 2, 11, 12 and 15, Okamoto et al. teach a method comprising:

(a) a step of designing probes for detecting a target substance (Fig. 4);

(b) a step of synthesizing each of the designed probes (page 440, second paragraph; page 441, second paragraph; Okamoto et al. do not specifically teach synthesizing the probes, but since they had them, they inherently had to be synthesized.);

(c) a step of individually purifying the synthesized plural probes (page 440, second paragraph; page 441, second paragraph; Okamoto et al. do not specifically teach purifying the probes, but since they had them, they inherently had to be synthesized and purified after synthesis.);

(d) a step of obtaining probe information on each purified probe (page 440, second paragraph; page 441, second paragraph; Okamoto et al. do not specifically teach obtaining probe information, but since they had them, they inherently had to be synthesized and purified after synthesis, therefore, they knew they had purified probes, i.e., obtained information about the probes.);

(e) a step of judging "good" or "not good" state of synthesis and purification in each purified probe according to the obtained probe information and a predetermined criterion (page 440, second paragraph; page 441, first and second paragraph; page 438, 7$^{th}$ paragraph; Fig. 2; where the probes' integrity was determined using HPLC after deposition onto a surface);

(f) a step of repeating the foregoing steps (b) to (e) on the purified probe of which state of synthesis and purification is judged as "not good", thereby obtaining "good" state of synthesis and purification in all the purified probes Okamoto et al. teach repeating the steps with different probes

(page 440, second paragraph; page 441, first and second paragraph; page 438, 7th paragraph; Fig. 2).);

(g) a step of individually dissolving each purified probe judged as "good" in a solvent for ejection to a carrier, based on at least a part of the probe information obtained in (d), in a predetermined concentration and storing each obtained probe solution in an individual storing container (page 438, paragraphs 6 and 7; page 439, second paragraph);

(h) a step of transferring each probe solution stored in the storing container to another container equipped in an apparatus for deposition onto the carrier (page 438, 7th paragraph; page 439, second paragraph; inherent in the fact that dissolution was not done in the ink-jet printer);

(i) a step of applying a surface treatment for fixing the probe to the carrier (page 438, last paragraph; page 439, first paragraph; page 441, fourth paragraph);

(j) a step of depositing the probe solution onto a treated surface of the carrier by a method including following steps, thereby forming a plurality of mutually independent probe fixation areas;

(j-2) a step of depositing the plural probe solutions onto the carrier judged as "good" by using the apparatus for deposition such that probe deposition area independent for each probe solution are arranged as spots of liquid droplets (page 439, second and third paragraphs);

(j-3) a step of executing an inspection, concerning a formed state of the probe deposition area, on the carrier on which the probe deposition area is formed, and judging "good" or "not good" state of the deposition according the result of the inspection and a predetermined criterion (page 439, paragraphs 4, 7; Fig. 3; where the spot distribution and shape were examined);

(j-4) a step of executing, on the carrier having the probe deposition area judged as "good", a fixation of the probe to the surface of the carrier thereby obtaining a probe carrier (page 439, second and third paragraphs);

(j-5) a step of executing an analytical inspection on the probe in at least one of the plural probe fixation areas constituted of probes fixed on the carrier; and (j-6) a step of judging "good" or "not good" state of the produced probe carrier according to the result of the analytical inspection and a predetermined criterion (page 439, paragraphs 4, 7; Fig. 3; where the spot distribution and shape were examined, also Fig. 5 and 6, where the hybridization reactions to proper probes were examined).

Regarding claim 3, Okamoto et al. teach nucleic acid probes (page 440, second paragraph; Fig.4).

Regarding claim 5, Okamoto et al. teach detecting purity of nucleic acid probes (page 440, second paragraph; page 441, first and second paragraphs).

Regarding claim 7, Okamoto et al. teach covalent bonding of nucleic acid probes (page 438, last paragraph; page 439, first paragraph).

Regarding claim 8, Okamoto et al. teach inkjet apparatus with single and plural ink jet nozzles (page 439, paragraphs 2 and 8).

B) Okamoto et al. teach 64 purified probes, but do not teach 100 or more kinds of probes, or deposition of probes using inkjet apparatus having 100 or more inkjet nozzles and solution containers.

C) Chen et al. teach preparation of an array with at least 1000 probes by printing the array on a substrate using a print head which contains at least 1000 nozzles and a corresponding number of solution reservoirs (Fig. 4; page 2, lines 3-9; page 3, lines 22-31; page 5, lines 9-33; page 7, lines 23-29; page 18, lines 1-13).

Chen et al. teach inspection of the fabricated microarray using optical methods (page 25; page 26, lines 1-7; Fig. 10, 11)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the printing head configuration of Chen et al. in the fabrication of microarrays by inkjet printing of Okamoto et al. The disclosure of Okamoto et al. provides a proof of principle that oligonucleotide microarrays can be printed using inkjet printer. Chen et al. suggests printing microarrays using print heads with a large number of nozzles and independent solution containers. As would have been appreciated by one of ordinary skill in the art at the time of the invention, such configuration would have allowed printing of a single array in one step. Further, multiple copies of the same probe arrangement could be made easily, and reagents conserved, since no cleanup of nozzles between the different solutions would be required. Finally, in the configuration where a separate solution container was provided for each print nozzle a chance of cross-contamination between the different probe solutions was minimized. The expectation of success is provided by Silverbrook, who teaches inkjets with 512, 2048, 5120 or 51,200 printing nozzles for high-resolution printing (col. 26, Table 1).

D) Regarding step (j-1), Okamoto et al. do not teach inspecting the carrier after the surface treatment.

E) Regarding claims 1, 2, 11, 12 and 15, Rava et al. teach quality control process for manufacturing biochips (page 1, lines 1-16; page 6, lines 6-18; page 14, lines 12-23; page 15, lines 1-2). Rava et al. specifically teach that each of the steps of array manufacturing can be subject to a quality control before further processing (page 17, lines 5-8) and testing of substrates after they were coated with xilane but before attachment of oligonucleotides (page 17, lines 9-14).

F) Park specifically teaches quality control analysis of fabricated DNA microarrays (Fig. 3, 5; col. 17, lines 33-67; col. 18-20), where the following parameters are analyzed: signal area (col. 17, lines 55-67; col. 18, lines 1-4), spot area (col. 18, lines 5-30), degree of ellipticity (col. 18, lines

31-58), square perimeter-to-spot area ratio (col. 18, lines 59-67; col. 19, lines 1-5); difference in the intensity of contamination regions versus signal region (col. 19, lines 6-13); deviation of spot's center location from canonical location (col. 19, lines 14-28), degree of alignment between sub-grids (col. 19, lines 29-54), uniformity in the distance between sub-grids (col. 19, lines 55-67 and col. 20, lines 1-12), variation in the identified background (col. 20, lines 13-34), determination of missing sub-grids (col. 20, lines 35-42) and parallelism of rows and columns (col. 20, lines 43-56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the methods of quality control of Park and Rava et al. in the chip production process of Okamoto et al., Chen et al. and Silverbrook. The motivation to do so is provided by Rava et al. (page 1, lines 6-13):

"Typically, the quality control testing of the items to be manufactured is performed at the point the item of manufacture is completed. In the event that the representative sample of items fails the requisite standards, all the items that had been processed with samples which would be expected to have similar defects are rejected. When the basis for rejection exists because of a process which occurred several steps prior to the completion of the product, the further processes were performed unnecessarily, at a great expense of time and money."

G) None of the above references teach examining the surface of the carrier using contact angle measurement. However, as can be seen from the references cited below, contact angle measurement was commonly used in the art to determine quality of derivatized surfaces and their properties.

H) Sundberg et al. teach derivatization of solid supports used in the solid-phase synthesis of oligonucleotide or peptide arrays (Abstract). They teach that the following factors determine the quality of oligomer arrays: spacing of synthesis initiation sites, wettability of the surface and non-

specific binding of ligands and the ways in which these parameters affect the hybridization experiments (col. 10, lines 1-54).They teach using different functional groups for derivatization of the substrates and characterization of the derivatized surfaces using contact angle measurement (Fig. 2; Fig. 14; col. 5, lines 25-35; col. 20, lines 7-44). Example 2 (col. 20, lines 52-67, col. 21, lines 1-35) describes determination of density of functional groups on the surface using fluorescent labels, whereas col. 21, lines 37-59 describe determination of chemical coupling efficiency.

The wettability of surfaces created with different functional groups by contact angle measurement is described in col. 20, lines 60-67 and col. 21. Finally, the quality determination of the final product is determined using an assay which determines a degree of non-specific–binding to the array surface (col. 23, lines 1-60).

I) Strother et al. teach creation of derivatized surfaces in order to create molecular arrays (Abstract). They teach derivatization of unoxidized carbon, silicon and germanium substrates with ω-modified alkenes and further attachment of oligonucleotides to such surfaces (col. 5, lines 45-67; col. 6; col. 7, lines 1-62). They teach quality control of every step of the surface derivatization process (col. 8, lines 1-64), where contact angle measurements were performed to determine the extent of deprotection of the surface (col. 8, lines 46-64).

Strother et al. also teach quality control characterization of the surfaces finally derivatized with nucleic acids: detection of hybridization specificity (col. 8, lines 65-67; col. 9, lines 1-15), surface density of attachment sites (col. 9, lines 16-67) and stability under conditions of repeated hybridization (col. 9, lines 65-67; col. 10, lines 1-27).

J) Corn et al. teach a method of producing biomolecular arrays on metal surfaces (Abstract) in a process outlined in Fig. 1 and described in col. 3, lines 15-67; col. 4, lines 1-64; col. 6, lines 49-67; col. 7-9; and col. 10-lines 1-39). Corn et al. teach the following tests of the quality of surfaces:

i) after step (1), detection of a PM-FTIRRAS spectra (col. 11, lines 52-63; Fig. 3A) to determine the degree of amino group protonation and measurement of contact angle to determine the degree of surface hydrophobicity (col. 11, lines 64-67; col. 12, lines 1-6; col. 7, lines 36-60);

ii) after step (2), again detection of a PM-FTIRRAS spectra (Fig. 3B) to determine the degree of amino group protection and measurement of contact angle to determine the degree of surface hydrophobicity (col. 8, lines 15-37);

iii) after step (6), detection of a PM-FTIRRAS spectra (Fig. 3C) to determine the degree of protecting group removal (col. 9, lines 51-61);

iv) after step (7), detection of the degree of binding of PEG-NHS groups to deprotected amino groups using PM-FTIRRAS spectra (Fig. 3D) and measurement of contact angle to determine the degree of surface hydrophilicity, as well as measurement of a thickness of the derivatized film (col. 10, lines 8-34) and the degree of non-specific binding (col. 10, lines 35-39).

K) Maxim et al. used measurement of contact angle and background fluorescence to examine the influence of materials used as storage containers on the properties of derivatized surfaces used to make biomolecular arrays (col. 1, lines 43-58; col. 6, lines 20-49; Table I; col. 7, lines 29-67; col. 8, lines 29-40; Fig. 2 and 3).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the measurement of contact angle as described by Sundeberg et al., Strother et al., Corn et al. and Maxim et al., to examine the quality of derivatized array substrates in the method of Okamoto et al., Chen et al., Silverbrook, Rava et al. and Park et al. The motivation to do so is provided by Maxim et al., who state (col. 1, lines 43-56):

"The surface chemistry and the surface morphology of the microarray substrate is a factor that impacts the quality of microassay readings. The surfaces of both organic and inorganic

substrates are typically modified by the deposition of a coating or a polymeric monolayer film to improve binding or attachment of biomolecules, promote adhesion and lubrication, modify the electrical and optical properties of the substrate surface, and create electroactive films suitable for various optical and electronic sensors and devices. Poor quality substrates result in low DNA binding efficiency, poor spot morphology, and fluorescent background that can be unacceptably high and nonuniform. Microarray substrates are susceptible to damage and degradation of the surface chemistry if they are not stored properly."

Therefore, as exemplified by the above references, contact angle measurements can be made to judge the degree of surface modification after every step of surface derivatization or to determine surface degradation after prolonged storage, in either case affording another level of quality control which is inexpensive to perform and prevents use of substrates with insufficient quality.

9. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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